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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 August 2000 (21.08.00)	
International application No. PCT/CA99/01189	**Applicant's or agent's file reference** 1038-999
International filing date (day/month/year) 15 December 1999 (15.12.99)	**Priority date** (day/month/year) 15 December 1998 (15.12.98)
Applicant LOOSMORE, Sheena, M. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 July 2000 (10.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/CA 99/01189

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/102 A61K39/116 A61K39/295 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BIOSIS, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. BARENKAMP: "Immunization with high-molecular weight adhesion proteins of nontypeable H. influenzae modifies experimental otitis media in chincillas" INFECT. IMMUN., vol. 64, no. 4, 1996, pages 1246-1251, XP002142962	1-3
Y	Abstract, last sentence. Discussion, last paragraph.	4-26
X	S. LOOSMORE AT AL.: "The H. influenzae Htra protein is a protective antigen" INFECT. IMMUN., vol. 66, no. 3, 1998, pages 899-906, XP002142963	1-3
Y	Discussion, last paragraph.	4-26

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2000	07/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skelly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/CA 99/01189

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 00149 A (MICROCARB INC.) 6 January 1994 (1994-01-06) claims 1-4,28-30	1
A	WO 97 36914 A (BARENKAMP) 9 October 1997 (1997-10-09) page 7, line 1 - line 4 page 20, line 15 -page 25, line 10	1-26
A	WO 96 03506 A (CONNAUGHT LABORATORIES LED) 8 February 1996 (1996-02-08) page 6, line 29 -page 7, line 10 page 14, line 33 -page 15, line 14	1-26

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...onal Application No
PCT/CA 99/01189

Patent document cited in search report	Publication dat	Patent family member(s)	Publication date
WO 9400149 A	06-01-1994	US 5843463 A	01-12-1998
		AT 176989 T	15-03-1999
		CA 2098598 A	22-06-1992
		DE 69130955 D	08-04-1999
		DE 69130955 T	01-07-1999
		EP 0565590 A	20-10-1993
		ES 2131066 T	16-07-1999
		JP 6508346 T	22-09-1994
		WO 9210936 A	09-07-1992
		US 5721115 A	24-02-1998
		US 5679547 A	21-10-1997
		CA 2138765 A	06-01-1994
		EP 0647139 A	12-04-1995
		JP 2805174 B	30-09-1998
		JP 7509693 T	26-10-1995
WO 9736914 A	09-10-1997	US 5977336 A	02-11-1999
		AU 2587397 A	22-10-1997
		CA 2259133 A	09-10-1997
		EP 0900232 A	10-03-1999
WO 9603506 A	08-02-1996	US 5506139 A	09-04-1996
		US 5939297 A	17-08-1999
		US 5869302 A	09-02-1999
		AU 687619 B	26-02-1998
		AU 3337695 A	22-02-1996
		BR 9506272 A	12-08-1997
		CA 2171611 A	08-02-1996
		CN 1136328 A	20-11-1996
		EP 0729513 A	04-09-1996
		NZ 291750 A	24-10-1997
		US 6025342 A	15-02-2000
		US 6020183 A	01-02-2000
		US 5665353 A	09-09-1997
		US 5935573 A	10-08-1999
		US 5656436 A	12-08-1997
		US 5981503 A	09-11-1999
		US 5962430 A	05-10-1999

1287

PATENT COOPERATION TREATY

PCT

REC'D 21 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1038-999		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/01189	15/12/1999	15/12/1998
International Patent Classification (IPC) or national classification and IPC A61K39/102		
Applicant CONNAUGHT LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/07/2000	16.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giry, M Telephone No. +49 89 2399 7328

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/01189

I. Basis of the r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-24	as originally filed				

Claims, No.:

9-21	as originally filed				
1-8,22-26	as received on	22/12/2000	with letter of	22/12/2000	

Drawings, sheets:

1/15-15/15	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 25 and 26.

because:

   ☒ the said international application, or the said claims Nos. 25 and 26 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inv ntive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	26
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R It m III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25 and 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT). See Item V-4.1 below.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 - **Reference** is made to the following documents :

D1 : S. Barenkamp : 'Immunization with high-molecular weight adhesion proteins of nontypeable *H. influenzae* modifies experimental otitis media in chinchillas' Infect. Immun., vol. 64, no. 4, 1996, pages 1246-1251

D2 : S. Loosmore et al. : 'The *H. influenzae* HtrA protein is a protective antigen' Infect. Immun., vol. 66, no. 3, 1998, pages 899-906

D3 : WO 96 03506 A, 8 February 1996

2 - **Novelty** - Art. 33(1) and (2) PCT :

2.1 The prior art document D1 reports on immunization with high molecular weight adhesion proteins of non typeable *Haemophilus influenzae*. A mixture of the purified native adhesins HMW1 and HMW2 with adjuvant was used as a vaccine in the chinchilla model of otitis media and proved to be protective against the disease (Abstract ; p. 1248, col. 2, lines 4-6 ; p. 1250, col. 1, lines 37-47). Document D1 therefore appears to be novelty destroying for independent claim 26.

2.2 The available prior art documents disclose neither an immunogenic composition comprising at least two different antigens of *H. influenzae* at least one of which being an adhesin and the other not, nor an immunogenic composition comprising a *H. influenzae* Hin47 analog and a HMW protein of a non-typeable *H. influenzae* strain. Thus, the subject-matter of independent claims 1 and 6 can be considered as new.

2.3 Claims 2-5 and 24-25 depend on claim 1 and claims 7-25 are dependent on claim 6, and as such also meet the requirements of the PCT with regard to novelty.

3 - **Inventive step** - Art. 33(1) and (3) PCT :

3.1 Document D2 reports on the *H. influenzae* heat shock protein HtrA (also named Hin47, see in the description p. 3, line 23) and the generation of mutants of this protein that present an impaired protease activity (Abstract ; p. 902, col. 2, lines 1-29). The protective properties against *H. influenzae* induced diseases including otitis media, of the wild type and mutant recombinant proteins used in immunogenic compositions are also described (Abstract ; p. 902, col. 2, lines 46-48).

3.2 Document D3, which is regarded as the closest prior art document concerns analogs of *H. influenzae* Hin47 protein with a decreased protease activity (of less than 10% of that of the natural protein) but retaining the same immunogenic properties of natural Hin47 (claims 1-2). Preferred analogs have mutations at Ser197, His91 and/or Asp121 positions (claims 3-9). Document D3 also discloses immunogenic compositions containing said Hin47 analogs and their use for prophylactic, vaccine or diagnostic purposes (claims 41-45). Conjugate vaccines comprising the Hin47 analogs in association to *e.g.*, glycoconjugates can be applied to vaccinations to confer protection against diseases caused by any bacteria having polysaccharide antigens (p. 14, line 33 to p. 15, line 10). Combined vaccines contain material from various pathogens or from various strains of the same pathogen or from combinations of various pathogens (p. 18, lines 7-12). Alum can be used as an adjuvant in said compositions (p. 7, lines 4-6

; p. 17, line 1).
The present invention differs from document D3 in the immunogens employed to design the immunogenic composition for protecting against *H. influenzae*-induced disease. The problem to be solved by the present application can therefore be seen in providing alternative immunogenic compositions conferring protection against *H. influenzae* provoked diseases.

3.3 As mentioned above (see point 2.1), document D1 teaches an immunogenic formulation comprising *H. influenzae* adhesins HMW1 and HMW2. Furthermore, it was demonstrated that "the protection demonstrated by immunization with the HMW1/HMW2 proteins was not complete, and that no single bacterial antigen from *H. influenzae* has yet demonstrated full protection in the chinchilla otitis model" (document D1, p. 1250, col. 1, line 48 to col. 2, line 2), and that "HtrA/Hin47 protein is a protective antigen" (documents D2 and D3, see points 3.1 and 3.2). Therefore, even if it is not suggested in any of the cited prior art documents as argued by the Applicant's Representative, the skilled person would regard it a normal obvious design procedure to combine two different types of *H. influenzae* antigens, *i.e.* adhesins from document D1 to the analogs of *H. influenzae* Hin47 disclosed in document D3, especially as a number of commercially successful vaccines are based on the use of two antigens from the same pathogen, thereby arriving at the compositions disclosed in claims 1-5 and 6-15. Thus, the subject-matter of claims 1-15 cannot be considered as involving an inventive step.

3.4 Whereas document D1 discloses native HMW1 and HMW2 (Abstract ; p. 1248, col. 2, lines 4-6 ; p. 1250, col. 1, lines 37-47), recombinant analogs of Hin47 protein are described in document D2 (p. 902, col. 2, lines 1-29) and document D3 (claims 26-38). Therefore, claims 16-17 do not contain any additional features which, in combination with the features of claim 15 to which they refer, meet the requirements of the PCT in respect of inventive step.

3.5 The subject-matter of claims 18-19 cannot be regarded as inventive since not only the addition of an adjuvant to an immunological composition falls within customary practice for the skilled person, but also the use of alum as an adjuvant has already been mentioned in documents D2 (901, col. 1, lines 12-13) and D3 (see point 3.2

above).

3.6 Document D1 specifies HMW1/HMW2 doses from 40 µg (p. 1248, col. 2, line 7), document D2 indicates immunization with 30 µg of HtrA (p. 901, col. 1, line 12), document D3 teaches that the quantity to be administered depends on the subject to be treated and that the suitable dosage ranges are readily determinable by one skilled in the art and may be of the order of micrograms of the Hin47 analogs (p. 17, lines 29-33). Hence, the ranges disclosed for both antigens in claim 20 cannot be considered as involving an inventive step.

3.7 The immunogenic compositions as featured in claims 21-23 cannot be regarded as involving an inventive step since the "combination of a multiple-component mixture providing the highest level of protection against disease" has already been suggested in document D1 (p. 1250, col. 2, lines 53-56) and mentioned in document D3 (see point 3.2).

3.8 The subject-matter of claim 24 cannot be considered as involving an inventive step for the use of said composition as a vaccine having already been disclosed in document D3 (see point 3.2).

3.9 In the light of document D1 (see point 2.1) and document D3 (see point 3.2) that disclose said immunogenic compositions for immunization purposes , the method of immunizing a host against disease caused by *H. influenzae*, subject-matter of independent claim 25 cannot be regarded as involving an inventive step.

4 - **Industrial applicability** - Art. 33(1) and (4) PCT :

4.1 Claims 25 and 26 concerning a method of immunizing and the manufacture of a vaccine relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT). See also the PCT Guidelines IV-2.5.

4.2 The subject-matter of claims 1-24 appears to be industrially applicable.

Re Item VII

Certain defects in the international application

a - The expression "incorporated herein by reference" employed *e.g.* on p. 1, line 19 of the description is not allowed as the application should be self-contained (Art. 5 and Rule 9.1(iv) PCT, see also PCT Guidelines II-4.17).

b - The vague and imprecise statement "scope of the invention" *e.g.* on p. 12, line 30 of the description implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity when used to interpret them. Such expressions are not allowed (Art. 6 PCT, PCT Guidelines III-4.3a).

Re Item VIII

Certain observations on the international application

a - Claims 7-8 and 21 do not meet the requirements of Art. 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem.

b - The term "substantially" used in claim 9 has no well-recognized meaning and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of the said claim unclear (Art. 6 PCT).